

ABSTRACTS

This section of the JOURNAL is published in collaboration with the two abstracting Journals, ABSTRACTS OF WORLD MEDICINE and OPHTHALMIC LITERATURE, published by the British Medical Association. The abstracts are divided into the following sections: Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous. After each subsection of abstracts follows a list of articles that have been noted but not abstracted. All subsections will not necessarily be represented in each issue.

SYPHILIS (Clinical)

Syphilis in Turkey. (Syphilis in der Türkei). LÜTFU TAT, A. (1960). *Hautarzt*, **11**, 507. 1 fig., 5 refs.

This paper from the University Dermatological Clinic, Ankara, reviews the history of syphilis in Turkey, describes the measures taken to combat it, and discusses the incidence of the disease during the past two decades. The disease is said to have been brought to Turkey by the Jews in the 16th century, but its incidence remained low until the beginning of the 20th century, when there was a very marked increase. In 1925 measures to deal with syphilis were introduced on a nation-wide scale for the first time. The country was divided into regions in each of which there was a specialist in venereology and dermatology responsible to the Ministry of Health, while four or five physicians with special training in the subject were attached to each regional office. Clinics have been planned so that they are not more than one hour's travelling distance for the majority of the population even in isolated rural areas.

As a result of these measures the incidence of syphilis has fallen during the past two decades. As in other countries the number of cases of early infectious syphilis increased during the Second World War, but the total number of cases of the disease in all stages actually fell during that period. Since 1949 there has been a steady decline in the number of recorded cases and in fact cases of early syphilis are now so rare that there is difficulty in finding enough patients for demonstration to medical students.

The author attributes this satisfactory situation to the active measures taken to combat the disease by the Ministry of Health.

R. D. Catterall

Atypical Clinical and Serological Features of Primary Syphilis at the Present Time. (Atypies cliniques et sérologiques actuellement observées au cours de la syphilis primaire.) MIDANA, M. A. (1960). *J. Méd. Lyon*, **41**, 1607.

Syphilitic Aortitis: A Diagnostic Problem. TORRES-GOMEZ, J. M., and DE JESUS, M. (1960). *Bol. Asoc. méd. P. Rico*, **52**, 361. 11 figs, 3 refs.

Organ Luetin in Endemic Syphilis. (Organluetin bei endemischer Syphilis.) LUGER, A., and SCHMID, E. E. (1961). *Derm. Wschr.*, **143**, 333. 2 figs, 31 refs.

Syphilis: Review of the Literature, 1959-60. BEERMAN, H., NICHOLAS, L., SCHAMBERG, I. L., and GREENBERG, M. S. (1961). *Arch. intern. Med.*, **107**, 121. 103 refs.

SYPHILIS (Therapy)

Results of Treatment of Syphilis with a Prolonged Course of Penicillin Totalling 14.4 mega units. (Über Resultate der Penicillinbehandlung der Syphilis mit einer protrahierten Kur von 14.4 Millionen Einheiten.) OBEID-RUGGLI, V. M. E. (1960). *Schweiz. med. Wschr.*, **90**, 820. 16 refs.

This paper from the university of Zürich reports the results of treating 107 syphilitic patients with a protracted course consisting of three intramuscular injections, each of 600,000 units procaine penicillin, weekly for eight weeks, making a total dose of 14.4 mega units. The series included twenty cases of primary syphilis, 21 of secondary syphilis, 47 of latent infection, three of symptomatic tertiary syphilis, five of late congenital syphilis, and eleven of neurosyphilis. The patients suffering from neurosyphilis received preliminary bismuth injections before starting the course of penicillin. Follow-up ranged from 3 to 10 years and during this period no clinical relapses were observed. All the cases of primary and secondary syphilis were clinically cured and the serological tests became normal in those which were initially sero-positive; in the cases of late syphilis reversal did not always occur [as would be expected—as titre estimations were not carried out assessment of the results of treatment in these cases, and especially in those of latent syphilis, is difficult or impossible].

Follow-up of the cases of neurosyphilis was incomplete and some of the patients received more than one course

of treatment. In those in which the cerebrospinal fluid was examined after treatment there was marked improvement in the findings or a complete return to normal. The author concludes that, although an observation period of 3 to 10 years is insufficient for ultimate conclusions to be drawn, this form of protracted penicillin therapy is justified in the treatment of syphilis, whether it be of the early infectious form or late syphilis. He recommends that in cases of neurosyphilis the treatment should be repeated on one or two subsequent occasions. *R. D. Catterall*

SYPHILIS (Serology)

New and Improved Antigen Suspension for Rapid Reagin Tests for Syphilis. PORTNOY, J., and GARSON, W. (1960). *Publ. Hlth Rep. (Wash.)*, **75**, 985. 5 refs.

The antigen suspension used for the rapid plasma reagin (R.P.R.) test for syphilis, using unheated plasma or serum, is made by resuspending centrifuged V.D.R.L. slide-test antigen in choline chloride. As originally described (*Publ. Hlth Rep. (Wash.)*, 1957, **72**, 761; *Abstr. Wld Med.*, 1958, **23**, 254) the suspension was said to be stable for at least a week, but subsequent work at the Venereal Diseases Research Laboratory, Chamblee, Georgia, has shown that some batches remain stable for up to 18 months. It was found that loss of reactivity is due to an oxidative process catalysed by cations.

In this study, undertaken to determine means of preventing this decline in reactivity, a series of antigen suspensions were prepared and contaminated with various cations and hydrogen peroxide and their stability determined by serial tests on pooled reactive human serum, using freshly prepared R.P.R. antigen as a control. On storage at room temperature antigens to which salts of copper, iron, magnesium, or zinc were added lost activity in 1 to 2 weeks, the loss being most rapid with copper sulphate. It was then shown that this deterioration could be prevented by the addition of sodium calcium-edetate (EDTA) as a chelating agent and that this agent was active in inhibiting deterioration for up to 3 weeks in a dilution as low as $1 \cdot 25 \times 10^{-4} M$. In the light of these findings it is recommended that EDTA should be incorporated in R.P.R. antigen suspensions. After precipitating the V.D.R.L. antigen and centrifuging, the deposit should be resuspended to the original volume in a solution composed as follows: 2.5 ml. of 0.1 M EDTA in distilled water (pH 7.0), 5 ml. of 40 per cent. choline chloride in distilled water, 10 ml. of 0.02 M phosphate buffer (pH 6.9) with 0.2 per cent. merthiolate, and 2.5 ml. distilled water.

The authors report that R.P.R. antigens prepared by this method were stable for at least 8 months at refrigerator temperatures and for lesser periods at room temperature or at 37°C. In tests in parallel with standard R.P.R. antigen, suspensions so prepared were found to be only slightly less reactive. The omission of sodium chloride from the suspending fluid gave a finer dispersion of particles with non-reactive specimens. *A. E. Wilkinson*

Biologic False Positive Reactions for Syphilis. KNOX, J. M., and BRITAIN MOORE, M., Jr. (1961). *Sth. med. J. (Bgham, Ala.)*, **54**, 281. 20 refs.

Experience with a New Plasma Test for the Diagnosis of Syphilis (R.P.R. "Rapid Plasma Reagin Test"). (Esperienze su un nuovo test per la diagnosi della sifilide sul plasma (R.P.R.: "Rapid Plasma Reagin Test"). SPAGNOLI, U., and MANNUCCI, E. (1960). *Ann. Sclavo*, **2**, 645. 6 refs.

Sero-diagnosis of Syphilis. Comparative Study of the "Classic" Reactions and the Reiter Protein Complement-Fixation Test. (Sérodiagnostic de la syphilis. Étude comparative des réactions "classiques" et de la fixation du complément avec l'antigène protéique du treponème Reiter.) VOGELSANG, TH. M., PILLOT, J., and FAURE, M. (1961). *Ann. Inst. Pasteur*, **100**, 190. 24 refs.

Sensitivity of Reiter Protein Complement-Fixation and Standard Serologic Tests: Comparison and Correlation with Clinical Findings in Syphilis. PARISER, H. (1960). *Sth. med. J. (Bgham, Ala.)*, **53**, 1543. 14 refs.

Action of Lysozyme on Reiter's Treponeme cultivated *in vitro*. (Azione del lisozima sul treponema di Reiter coltivabile *in vitro*.) COSTA, A. L., and CASCIANO, A. (1960). *Dermatologia (Napoli)*, **11**, 194. 5 figs.

Separation of the Wassermann Reagents by Cellulose Column Chromatography of Serum. LAURELL, A. B., and MALMQUIST, J. (1961). *Acta path. microbiol. scand.*, **51**, 187. 14 refs.

Problems of the Local Incubation of *Treponema Pallidum* in Syphilis in the Rabbit. (Problèmes de l'incubation locale de *Spirocheta pallida* dans la syphilis du lapin.) GASTINEL, P., VAISMAN, A., DUNOYER, F. (1961). *Ann. Inst. Pasteur*, **100**, 1. 2 figs, 7 refs.

SYPHILIS (Experimental)

Results obtained with Cortisone in Experimental Syphilis. (À propos des résultats obtenus par l'emploi de la cortisone en syphilis expérimentale.) GASTINEL, P., COLLART, P., VAISMAN, A., HAMELIN, A., and DUNOYER, F. (1960). *Ann. Derm. Syph. (Paris)*, **87**, 612. 6 refs. (Also 1961, *Proph. sanit. morale*, **33**, 41. 6 refs.)

GONORRHOEA

Concentrated Culture of Gonococci in Clear Liquid Medium. GERHARDT, P., and HEDEN, C. G. (1960). *Proc. Soc. exp. Biol. (N.Y.)*, **105**, 49. 1 fig., 3 refs.

It has been shown at the University of Michigan Medical School that dense suspension of gonococci can be obtained by growing them in a thin layer of liquid over a layer of solid medium. The liquid phase consisted of 1.5 per cent. proteose peptone No. 3 (Difco), 0.2 per cent. dextrose, 1.0 per cent. soluble starch, 0.5 per cent.

sodium chloride, 0.3 per cent. $\text{Na}_2\text{HPO}_4 \cdot 2\text{H}_2\text{O}$, and 2 per cent. gelatine. The final pH was 7.3. The broth was clarified by filtration through Celite while hot. For the solid underlay 2 per cent. agar was added.

100 ml. solid medium in a conical flask was overlaid with 25 ml. liquid broth, and after inoculation was incubated in an atmosphere of 10 per cent. CO_2 in a rotary shaker at 37°C . The amount of growth was measured by turbidity or by direct count. Cell counts of 3.3 billions/ml. were obtained in this biphasic system, while in control tests with fluid medium alone the density reached 0.84 billions/ml. It was found that either starch or gelatine, but not both, could be omitted from the overlying broth when this was equilibrated with the complete solid medium for 24 hrs before inoculation. When distilled water was similarly equilibrated instead of broth, densities as high as 2.2 billions/ml. were obtained, sufficient nutrient factors to support luxuriant growth having presumably diffused out of the underlying agar layer.

A. E. Wilkinson

Effect of Added Calcium on Treponemal Immobilization.

CHORPENNING, F. W., and BEERS, D. B. (1960). *J. Immunol.*, **85**, 240. 17 refs.

The enhancing effect of optimal concentrations of calcium ion (Ca^{++}) on immune haemolysis has been known for some time. If this is due to protective action or "sparing" effect on complement component C'_1 it should be as effective in specific (immune) immobilization as in complement fixation. In order to examine this hypothesis experimentally quantitative treponemal immobilization (T.P.I.) tests were performed, with and without added Ca^{++} , under rigidly controlled conditions of time and temperature and concentrations of antigen, antibody, and C'_1 . The titres so obtained were compared to ascertain whether the addition of calcium caused an increase. In addition, complement titrations in terms of $\text{C}'\text{H}_{50}$ activity were performed on the test mixtures at the beginning and the end of the test period.

When complement concentrations and other factors were the same, immobilization titres were consistently increased by the addition of ionic calcium. This effect was accompanied by the presence of increased haemolytic activity in the residual test mixtures after incubation. The addition of calcium had no adverse effects on the results of the T.P.I. test or on treponemal survival.

R. R. Willcox

Sensitivity *in vitro* of Gonococci to Three Penicillins.

ØDEGAARD, K. (1960). *Acta dermat.-venereol. (Stockh.)*, **40**, 504. 1 fig, 11 refs.

Study of Current Sensitivity of the Gonococcus to the Principal Antibiotics. (Étude de la sensibilité actuelle du gonocoque aux principaux antibiotiques.)

ROIRON, V., RASETTI-NICOD, G., and DUREL, P. (1961). *Ann. Inst. Pasteur*, **100**, 445. 2 figs, 25 refs.

Validity of Reports of Penicillin-resistant Gonococci.

GANGAROSA, E. J., and CARY, S. G. (1960). *J. Amer. med. Ass.*, **173**, 1808. 16 refs.

There have been a number of reports recently of an increasing incidence of penicillin-resistant gonococci. The present authors examine the evidence and urge restraint and caution in diagnosing penicillin-resistant gonorrhoea. They recall the observations of DeBord (*J. Lab. clin. Med.*, 1943, **28**, 710) on a species of bacteria, *Mimeae*, so-called because it is capable of mimicking the gonococcus, particularly if too much reliance is placed upon recognition of *Neisseria gonorrhoeae* by the Gram-staining reaction. None of the most recent reports have specifically excluded mimeae from bacteriological studies. Deacon (*J. Bact.*, 1945, **49**, 511) confirmed DeBord's findings by isolating mimeae from cases of so-called "penicillin-resistant" gonococcal infection, while Hughes and Carpenter (*Amer. J. Syph.*, 1948, **32**, 265) found that 91 per cent. of patients invalided out of the army because of infection with penicillin-resistant gonorrhoea had a urethritis from other bacterial causes. Indeed, these authors also demonstrated that the remaining cases of true gonococcal infection were in fact re-infections and that all the 6 strains of gonococci tested for penicillin sensitivity were inhibited by 0.08 unit of the antibiotic or less. Their observations were confirmed by Cohn and others (*Amer. J. Syph.*, 1949, **33**, 86), who suggested that some cases of resistance were due to the walling-off of the sites of infection, so that a higher dosage of penicillin was necessary to ensure adequate penetration.

The authors conclude that the case for true penicillin-resistant gonorrhoea is not yet proven, and that penicillin is still the treatment of choice.

Allene Scott

Cytology of the Conjunctival Fluid in the New-born, with Reference to Credé's Prophylaxis. [In English.]

NORN, M. S. (1960). *Acta ophthal. (Kbh.)*, **38**, 491. 5 figs, 7 refs.

In recent years the desirability of the practice of instilling silver nitrate into the eyes of the newborn has been disputed. The author, using his own quantitative pipette method, has examined the cell content of 170 samples of conjunctival fluid from sixty newborn infants (both conjunctivae) before and after Credé's prophylaxis with a 0.66 per cent. solution of silver nitrate. Examination showed that before the instillation only a few children had neutrophilia, whereas after it there was epithelial desquamation followed by neutrophilia which, in one-third of the infants, persisted for up to 3 days. Neutrophilia and purulent conjunctivitis after the 5th day, however, is due to bacterial infection and should receive appropriate treatment. Other methods of prophylaxis are briefly discussed. Tests on adults with "rhodalon" (0.1 per cent. benzalcon chloride) showed that it provoked a similar cytological response and "desogen" a less pronounced reaction. The author points out that, remarkably, lymphocytosis was never found in newborn infants, although in a previous study he had shown it to be present in all normal children aged between 3 and 10 years.

G. von Bahr

Comparison of Ocular Reactions with the Use of Silver Nitrate and Erythromycin Ointment in Ophthalmia Neonatorum Prophylaxis. CHRISTIAN, J. R. (1960). *J. Pediatr.*, **57**, 55. 16 refs.

Eyedrops of 1 per cent. silver nitrate were given to 2,359 newborn infants at birth and they were compared with 1,933 infants who had erythromycin ointment.

Ocular reactions occurred in 10 per cent. of the silver nitrate series and in 4 per cent. of the erythromycin series. Cultures were made from those whose reaction included a discharge: 206 out of 237 cases given silver nitrate had sterile cultures, as had 65 out of 78 given erythromycin.

W. E. S. Bain

NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS

Clinical Evaluation of Metronidazole: A New Systemic Trichomonocide. WATT, L., and JENNISON, R. F. (1960). *Brit. med. J.*, **2**, 902. 12 refs.

It is believed that local treatment of vaginitis caused by *Trichomonas vaginalis* often fails because extravaginal foci remain untouched. Durel and others (*Brit. J. vener. Dis.*, 1960, **36**, 21) have reported successful results in both men and women with a new imidazole derivative, metronidazole (1- β -hydroxyethyl-2-methyl-5-nitroimidazole). In the present paper the results obtained with metronidazole in fifty female patients treated at St. Mary's Hospital for Women, Manchester, for vaginitis due to *T. vaginalis* are described. The drug was given by mouth in a dosage of 600 mg. daily for one week. Relief from irritation was rapid and there was a dramatic clinical improvement within a week in cases of recent onset. Chronic infections improved more slowly, but 44 of the patients showed no clinical or laboratory evidence of infection at the end of treatment. Side-effects, which were not usually severe, occurred in eleven patients, but it was necessary to discontinue treatment only in one patient who vomited when receiving 1,200 mg. daily. This high dosage was given to the six patients who did not respond initially, and three of them appeared to benefit. It is considered that the failure of treatment in the remaining three was not due to re-infection, but to poor absorption of the drug or to the greater resistance of the organism.

Janice Taverne

Treatment of Trichomoniasis with Metronidazole. MOFFETT, M. and MCGILL, M. I. (1960). *Brit. med. J.*, **2**, 910. 3 refs.

Metronidazole was given to 42 female patients attending out-patient clinics for the treatment of venereal disease in Glasgow who had vaginitis due to *Trichomonas vaginalis*. The first fourteen patients received 600 mg. by mouth daily for 10 days and one 0.5-g. pessary each night during that period, the next 24 received the same oral dosage but no pessary, and the remaining four were given the oral dosage for 7 days only. Complete relief of symptoms and absence of trichomonads on culture in Feinberg-Whittington medium indicated cure in forty of the patients. In one patient who was given both tablets

and pessaries there was no response even after further treatment for 10 days, and in another who had a very heavy infestation there was a relapse after 7 days' treatment. Of the 42 patients, six were pregnant. The presence of a cervical erosion did not interfere with the results, but it was noted that in three patients infection due to *Candida albicans* became more troublesome when *T. vaginalis* was controlled.

None of the patients has yet been observed for longer than 3 months, but the authors consider that the results justify a more extensive trial of the drug and that systemic administration is sufficient without local treatment.

Janice Taverne

Certain Epidemiological, Clinical, and Diagnostic Aspects of Trichomoniasis in the Male. [In Russian.] LJAHOVICKIJ, N. S. (1960). *Sovetsk. Med.*, **24**, 87. 16 refs.

Trichomoniasis is an important venereal disease which, in the male, is more common in the sexually active period of life and clinically presents in a great variety of forms, ranging from the acute to the asymptomatic. In the present study 190 infected males were divided into three groups suffering respectively from:

- (1) the acute form (4.7 per cent.);
- (2) the subacute or chronic form (60.4 per cent.);
- (3) the asymptomatic form (33.8 per cent.);
- (4) two healthy asymptomatic carriers.

In Group 3 the diagnosis was made on the finding of trichomonads in the urine during a routine examination for other reasons. All these patients had a low-grade chronic urethritis. It is urged that clinical investigation should always include microscopical examination of stained and unstained smears of the urethral discharge, urine, secretions of the prostate and seminal vesicles, and mucosal scrapings.

Cultural methods and microscopical techniques gave positive results in 77.7 per cent. and 83.3 per cent. of these cases respectively, the former being thus a useful adjunct to the latter. Complement-fixation tests showed no advantages and were found to be unsuitable. In 10.3 per cent. of the cases repeated laboratory examination was necessary. In eight cases the parasite was demonstrated in urethral scrapings and prostatic secretion but not in the urine, in nine cases in the urine and prostatic secretion but not in scrapings, in 34 cases in mucosal scrapings and urine but not in prostatic secretion, and in fourteen cases in the urine only. In five patients with non-gonococcal urethritis the parasite was found in the material obtained under direct vision from lacunae and Littre's glands during urethroscopy, although in three of these cases it could not be identified in the urine, the prostatic secretion, or urethral scrapings.

S. W. Waydenfeld

Systemic Treatment of *Trichomonas vaginalis* Infestation in Women: a Preliminary Report. REES, E. (1960). *Brit. med. J.*, **2**, 906. 3 refs.

This paper from the Liverpool Royal Infirmary describes the results of treatment with metronidazole in 39 female

patients suffering from infestation with *Trichomonas vaginalis*. The drug was given by mouth in a dosage of 600 mg. a day for 7 days to the patients and, to prevent re-infection, to their male partners. There was prompt clinical improvement within a week in the fourteen cases of acute infestation, negative cultures (in Feinberg-Whittington liquid liver medium) being obtained after 12 weeks. Most of the 19 patients with subacute infestation were cured by the end of the course, with negative cultures within 12 weeks but three of these did not become symptom-free; re-infestation with *T. vaginalis* and gonococci occurred in one patient, one had a persistent discharge associated with an infection by *Candida albicans*, and one did not show any clinical response to treatment, although cultures positive for *T. vaginalis* were obtained during the 8th week of observation. The remaining six patients were asymptomatic carriers and all except one, who was re-infected in the 6th week, were free from the parasite 12 weeks after starting treatment. There were five patients who complained of nausea, and a rash developed in one.

It is concluded that metronidazole is an effective remedy, although it is too early to assess its long-term value. A warning is given that the rapid disappearance of vaginal discharge after treatment may delay the diagnosis of co-existing gonorrhoea. *Janice Taverne*

Uveitis and Urogenital Disease in the Male. CATTERALL, R. D., and PERKINS, E. S. (1961). *Brit. J. Ophthalm.*, **45**, 109. 5 refs.

The authors report the examination of 211 male patients of whom 68.7 per cent. were found to have uveitis. Approximately one-third of these also had Reiter's syndrome and one-third had ankylosing spondylitis. The high incidence of prostatitis and ankylosing spondylitis in acute anterior uveitis differs markedly from posterior uveitis in which toxoplasmosis appears to be the chief aetiological agent. No definite organism has been found to cause the prostatitis. It is suggested that acute non-specific urethritis is an infection of venereal origin which may initiate a classical acute Reiter's disease. The uveal tract, the joints, and the prostate have a joint mesodermal origin. *A. G. Cross*

Relationship of Human Genital Pleuropneumonia-like Organisms to Arthritis complicating Urethritis. FORD, D. K. (1960). *Arthr. and Rheum.*, **3**, 395. 25 refs.

The present study was undertaken at the University of British Columbia, Vancouver, in the hope that primary isolation of pleuropneumonia-like organisms (PPLO) from the joint fluid of patients with Reiter's disease might be achieved by means of human amnion tissue culture instead of directly with agar media. A total of fifteen synovial exudates from twelve patients with arthritis and urethritis failed to show PPLO by the tissue-culture method, nor was any cytopathogenic change seen in the amnion preparations. In addition, 240 patients, men and women, attending a venereal disease clinic with a variety of urogenital conditions were investigated by this method. From these cases 75 PPLO strains were isolated, but no evidence was obtainable that PPLO were aetiologically

related to non-gonococcal urethritis or Reiter's syndrome.

G. W. Csonka

Special Psychological Features of Patients with Non-Gonococcal Urethritis. (Aspects psychologiques particuliers des malades atteints d'urétrite non-gonococcique.) SIBOULET, A. (1960). *Cah. méd. Auvergne*, No. 8, p. 355.

CHEMOTHERAPY

A New Synthetic Penicillin. DOUTHWAITE, A. H., and TRAFFORD, J. A. P. (1960). *Brit. med. J.*, **2**, 687. 11 refs.

In this paper and a series of six others [see following Abstracts] it is shown that methicillin ("BRL 1241"), a new synthetic antibiotic, is active against penicillin-resistant staphylococci, has a spectrum similar to that of benzylpenicillin, and is both stable and active in the presence of staphylococcal penicillinase. It is non-toxic, but is unstable in acid medium and therefore cannot be given by mouth.

The authors of the first paper, from Guy's Hospital, London, describe a clinical trial of methicillin on thirteen patients, five of whom were suffering from pneumonia, four from wound infections, and four respectively from bronchiectasis, extradural abscess, cerebellar abscess, and urinary infection. The drug was given in a dosage of 1 g. 4-hrly for 5 to 21 days, the patient with intracranial abscess requiring the drug for the longest period. No evidence of *Staphylococcus aureus* infection was detected in any patient after the end of treatment. The injections were as painful as those of benzylpenicillin and prolonged treatment caused local reactions. In one patient, not included in the series, who was sensitive to penicillin there was no reaction to a test dose of methicillin; however, an erythematous rash developed 36 hrs after receiving full dosage of the drug. The blood level of methicillin ranged from 18 to 21 µg. per ml. after 30 min. and gradually declined to 2 µg. per ml. by the fourth hour. Assay of the urine showed that 75 per cent. of the drug was excreted in one day.

Anne Tothill

A New Penicillin (BRL 1241) Active against Penicillin-resistant Staphylococci. KNOX, R. (1960). *Brit. med. J.*, **2**, 690. 14 refs.

The second paper in this series describes laboratory investigations carried out at Guy's Hospital Medical School, London, into the antimicrobial and bactericidal activity of methicillin, the effect of penicillinase on the antibiotic, and the action of methicillin on penicillinase formation. Attempts were also made to produce organisms which were resistant to the drug. The serial tube dilution test was used to compare the activity of methicillin, benzylpenicillin, phenoxymethylpenicillin, and "broxil" (phenethicillin) against several common pathogenic organisms. Methicillin was inhibitory to penicillin-resistant staphylococci in a concentration of 2 µg. per ml. but *Salmonella paratyphi* C, which is inhibited by 0.2 µg. penicillin per ml., was resistant to methicillin. The drug was moderately active against *Neisseria meningitidis* and highly active against the strains of streptococci tested.

Methicillin was equally effective whatever the size of the inoculum, a finding which is in direct contrast to benzylpenicillin, phenoxymethylpenicillin, and phenethicillin. On prolonged incubation (after 7 days) large inocula would grow in high concentrations of methicillin, and this effect is under investigation. Methicillin was not appreciably destroyed by staphylococcal penicillinase. In a concentration of 5 $\mu\text{g.}$ per ml. it had a bactericidal effect on both Oxford and penicillinase-producing (E_s) staphylococci. This was measured by the broth dilution technique followed by viable cell counts at intervals. Under appropriate conditions methicillin was lytic as well as bactericidal to both strains but, as with benzylpenicillin, lysis could be demonstrated only when the cells were in a metabolically active state. The drug was found to induce more penicillinase production in organisms already producing the enzyme, although it was not a substrate. By serial subculture in tubes containing methicillin attempts were made to train penicillin-resistant and penicillin-sensitive staphylococci to become resistant to the drug. This work is still in the preliminary stage, but after three subcultures of E_s staphylococci in increasing concentrations of the drug the organism was able to grow in a concentration of 18 $\mu\text{g.}$ per ml. and had reverted to the penicillin-sensitive state while no longer producing penicillinase. These findings indicated that the different penicillins have a varying range of antibacterial activity and must be considered separately.

Anne Tothill

Microbiological Studies on Sodium 6-(2:6-Dimethoxybenzamidop)penicillanate Monohydrate [BRL 1241] *in vitro* and in Patients. STEWART, G. T. (1960). *Brit. med. J.*, 2, 694. 6 figs, 4 refs.

In this third paper the results of sensitivity tests of methicillin against various organisms in liquid and solid media by colony counts of aliquots and by the disk method are reported from Queen Mary's Hospital for Children and the Medical Research Council Laboratories, Carshalton, Surrey. Assays of the antibiotic in body fluids were performed on large-scale assay plates seeded with the test organism, usually *Sarcina lutea*. The unknown fluid was compared in each assay with a range of controls in water, serum, plasma, and albumin, and the results were read from graphs. Urine was heated to minimize contamination and diluted 1:100 with water. The ascending technique was used for chromatography of the drug in urine; after an overnight run the chromatograms were dried and "developed" on assay-plates seeded with *S. lutea*.

A preliminary survey of the comparative sensitivities of *Staphylococcus aureus*, three strains of *Streptococcus pneumoniae*, *Proteus*, coliform bacilli, *Pseudomonas pyocyanea*, *Shigella*, *Salmonella*, *Haemophilus*, and *Clostridium welchii* to benzylpenicillin, phenoxymethylpenicillin, phenoxypionamidopenicillin, and methicillin was carried out. It was found that 43 per cent. of strains of *Staph. aureus* were completely resistant to 10 $\mu\text{g.}$ benzylpenicillin per ml., whereas all these strains were inhibited by this concentration or less of methicillin, and that 74 per cent. were inhibited by phenoxypionamidopenicillin.

The other pyogenic Gram-positive cocci were, in general, more sensitive to the natural penicillins than to the two synthetic ones. Group-A streptococci and pneumococci were uniformly sensitive to the synthetic penicillins and also the benzylpenicillin, but were mostly resistant to methicillin. Gram-negative bacteria, apart from some strains of *Haemophilus* were highly resistant to methicillin. *Staph. aureus* was sensitive to 1 to 2 $\mu\text{g.}$ of methicillin per ml., which was always bactericidal. At the optimum concentration of 2.5 to 5 $\mu\text{g.}$ per ml. one-half of the cells of the inoculum were killed in one hour and 90 to 95 per cent. in 2 hours. This action was uniform for all the strains tested. All four penicillins had bactericidal effect on all strains of *Streptococcus* tested. The bactericidal action of methicillin was less rapid than that of benzylpenicillin, but more complete. All strains of *Pneumococcus* were sensitive to all the penicillins. Methicillin in a concentration of 2.5 $\mu\text{g.}$ per ml. inhibited many of the penicillinase-forming strains of *Staphylococcus* even in the presence of a large inoculum. The authors state that the drug also acts as a penicillinase inducer and as a substrate and may suffer inactivation after 24 to 48 hrs of growth; it could also be completely inactivated by incubation with potent forms of penicillinase derived from *Bacillus licheniformis* and *B. cereus*.

Attempts were made to induce resistance in two strains of *Staph. aureus* and Group-A streptococci by repeated passage through solid and liquid media and *in vivo*. Acquired resistance did not develop and the colonies retained their normal morphological and biochemical properties on subculture on drug-free media. Methicillin did not have a synergic effect with any other penicillin. Individual samples of blood were taken from a number of children at various intervals after injection of a standardized dose of 100 mg. per kg. body weight daily. The inhibitory levels were 1 $\mu\text{g.}$ per ml. or higher and were detectable 4 hrs after injection, but not longer. Two-thirds of the dose was excreted in the urine unchanged within a few hours of injection, and most of the remainder was excreted in the bile. Hypersensitivity to the drug was shown in an adult volunteer who had previously reacted to benzylpenicillin; the course of the reaction was identical. Methicillin had an unusual activity against staphylococci, but against other organisms it was not as satisfactory as the natural penicillin.

Anne Tothill

Absorption and Excretion of a New Antibiotic [BRL 1241]. KNUDSEN, E. T., and ROLINSON, G. N. (1960). *Brit. med. J.*, 2, 700. 1 ref.

The fourth paper in this series describes investigations carried out at Beecham Research Laboratories, Brentford, Middlesex, designed to determine a suitable scheme of dosage of methicillin for therapeutic use. The antibiotic was assayed in body fluids, the cup-plate method being used. Before any studies in human beings were undertaken the drug was shown to be non-toxic to animals. In three healthy human subjects, a single injection of 100 mg. produced blood levels which were too low to be of any therapeutic value, reaching a maximum of 2.6 $\mu\text{g.}$ per ml. after one hour. In a second experiment three

healthy subjects received 100 mg. of the drug every 2 hours for three doses and one received 200 mg. initially and 100 mg. 2-hrly for two doses. Urine was collected from two subjects over a 6-hr period, and the urinary excretion of methicillin was 62 and 61 per cent. of the respective total doses. Serum levels were at a maximum (2.2 to 4.1 μ g. per ml.) 30 to 60 min. after injection.

A clinical evaluation of the antibiotic was then carried out on three patients with penicillin-resistant staphylococcal infection. The first patient, a man aged 28 with infection of the right hallux after surgical treatment, was given methicillin for 24 hrs only, during which time he received 2.6 g. in divided doses every 2 hrs. The maximum blood level of 9.5 μ g. per ml. was reached 5½ hours after the initial dose; 45 per cent. of the dose was excreted in the urine. No staphylococci were isolated from the wound after treatment. The second patient, a girl of 17, was suffering from coagulase-positive staphylococcal pneumonia which had failed to respond to most antibiotics. An initial dose of 450 mg. of methicillin was given intramuscularly, followed 2 hrs later by 600 mg. similarly administered. As she was receiving fluids intravenously 750 mg. of the drug was run in over 30 min. 3-hrly for 2 days; later 1 g. was infused over 15 min. every 3 hrs. The patient subsequently received 1 g. 4-hrly intramuscularly. At 36 hrs after the start of treatment the patient was afebrile and a chest radiograph showed clearing of basal pneumonia. The drug was continued for a further 14 days, a total of 100 g. being given. No toxic side-effects were observed. The serum methicillin level rose to 18 μ g. per ml. 3 hrs after the start of treatment and before intravenous infusion, a maximum of 46 μ g. per ml. being attained. The patient died from coliform septicaemia 14 days after the cessation of treatment; there was then no evidence of staphylococcal infection. The third patient, a man of 58 who was suffering from multiple boils, was given 1 g. of methicillin 4-hourly for 3 days, then 6-hrly for 3 days, after which there was complete resolution of the boils. It is concluded that 1 g. every 4 to 6 hrs intramuscularly is a suitable therapeutic dosage for adults.

Anne Tothill

Treatment of Experimental Penicillin-resistant Staphylococcal Lesions with BRL 1241. THOMPSON, R. E. M., WHITBY, J. L., and HARDING, J. W. (1960). *Brit. med. J.*, 2, 706. 3 figs, 7 refs.

At the Bland-Sutton Institute of Pathology, Middlesex Hospital, London, the authors of the sixth paper in this series infected mice with *Staphylococcus pyogenes* isolated from a case of staphylococcal pyaemia. The strain was sensitive to 1.6 unit benzylpenicillin per ml., 15 μ g. streptomycin per ml., 75 mg. tetracycline per ml., 3.2 μ g. chloramphenicol per ml., 0.4 μ g. erythromycin per ml., and 1.6 μ g. methicillin per ml. An inoculation of 0.2 ml. of a 1:2 dilution of a broth culture was given into the thigh muscles of each animal; a group of ten mice was used for each compound tested, with a control group. The diameter of the infected thigh was measured 24 hrs after inoculation and then daily for 4 days and finally on the 7th day, the results being expressed as the average

daily increase in diameter for the group. The dosage was 50 mg. methicillin per kg. body weight subcutaneously; five doses were given, the first immediately after infection and the others at 24-hr intervals. The infection was completely controlled in all the mice as shown by the absence of an increase in the diameter of the thigh. Similar experiments were carried out with a number of other antibiotics given at the same dose level. Erythromycin was the most effective on a weight-for-weight basis, followed by methicillin, streptomycin, and chloramphenicol; tetracycline and penicillin were relatively inactive. Methicillin was also given in dosages of 1 and 10 mg. daily for 7 days and also in a single dose of 50 mg.; the single dose and 10 mg. daily gave the most protection.

Anne Tothill

Sensitivity of *Staphylococcus pyogenes* to Benzylpenicillin and BRL 1241. THOMPSON, R. E. M., HARDING, J. W., and SIMON, R. D. (1960). *Brit. med. J.*, 2, 708. 1 fig, 6 refs.

The final paper in this series reports a study at the Bland-Sutton Institute of Pathology, Middlesex Hospital, London, of the sensitivity of *Staphylococcus pyogenes* to benzylpenicillin and to methicillin, a total of 118 strains of pathogenic organisms isolated from patients and staff being examined. Qualitative sensitivity tests were carried out on broth-agar slopes on which strips of filter paper impregnated with benzylpenicillin and methicillin were placed. All strains were sensitive to methicillin in a concentration of 1.6 to 3.2 μ g. per ml., but only 18 per cent. were sensitive to benzylpenicillin.

[Methicillin appears to be an ideal drug for the short-term treatment of staphylococcal infections, but there has not yet been enough experience of the effect of protracted courses of the drug for its value in this respect to be assessed.]

Anne Tothill

Report on Clinical Use of BRL 1241 in Children with Staphylococcal and Streptococcal Infections. STEWART, G. T., NIXON, H. H., and COLES, H. M. T. (1960). *Brit. med. J.*, 2, 703. 6 refs.

The authors of this article describe a clinical trial of methicillin in seventeen children suffering from staphylococcal infection. The responsible pathogen was isolated in each case and assayed for sensitivity to the antibiotic and to other substances. Of the seventeen infecting strains, thirteen were resistant to benzylpenicillin and seven belonged to Phage Type 80. One or more antibiotics had previously been given to twelve of the patients. A standard daily dosage of 100 mg. methicillin per kg. body weight was given intramuscularly for 5 days, except to one child with septicaemia who received 150 mg. per kg. per day in 4-hrly doses during 7 days of a 30-day treatment course. Clinical improvement was observed in fourteen patients, with complete cure in seven. There were two deaths during treatment, both in infants with severe Type-80 infection; one infant, aged 11 days, also had a tentorial tear, and the other, aged 4 months, had fibrocystic disease of the pancreas. Strains of staphylococcus recovered from

the patients retained their original sensitivity to methicillin. Streptococci were less sensitive to the drug than to benzylpenicillin, but one child who had bilateral suppurative otitis media and had not responded to penicillin or benzylpenicillin did so to methicillin, with clinical improvement 2 days after beginning treatment. The drug was also given to eleven additional children with sore throat or other streptococcal infections, ten of whom showed clinical improvement. Pain and tenderness at the site of injection were the only side-effects. During or just after treatment there was replacement of the coccal salivary flora by coliforms in several of the children, and two developed superficial infections with *Candida albicans*.

Anne Tothill

Penicillin V and Phenethicillin Potassium in Serum: Comparison of Concentrations and of Antibacterial Effects.

MARTIN, W. J., and NICHOLS, D. R. (1960). *Proc. Mayo Clin.*, **35**, 577. 11 refs.

At the Mayo Clinic the serum concentrations of phenoxymethylpenicillin and phenethicillin potassium after giving equal doses by mouth were estimated and the antibacterial effect of the serum was studied in 22 subjects. It was found that in eighteen of the 22 the concentration of phenethicillin potassium in the serum 2 hrs after administration of the last of four 6-hourly doses of 250 mg. was greater than that of phenoxymethylpenicillin after a similar dosage. Mean concentrations titrated by the cup-plate method with *Sarcina lutea* as the test organism were 2.67 µg. per ml. of serum after phenethicillin potassium and 1.65 µg. per ml. after phenoxymethylpenicillin. When the sera were tested against penicillin-sensitive staphylococci little difference was observed between the antibacterial activity of serum containing phenethicillin potassium and that containing phenoxymethylpenicillin. Against strains showing increased resistance to penicillin more sera containing phenethicillin potassium than sera containing phenoxymethylpenicillin were effective in eradicating growth *in vitro*, but frequently only when undiluted.

It is concluded that while phenethicillin potassium does not appear to represent any great advance in clinical therapeutics, it is probably the forerunner of "newer penicillin fractions of possible clinical application that will be produced synthetically".

A. Ackroyd

Absorption and Excretion of N-(pyrrolidinomethyl) Tetracycline. CRONK, G. A., BUCKWALTER, F. H., WHEATLEY, W. B., and ALBRIGHT, H. (1961). *Amer. J. med. Sci.*, **241**, 1. 8 figs, 4 refs.

PUBLIC HEALTH AND SOCIAL ASPECTS

Homosexuality and Venereal Disease. NICOL, C. S. (1960). *Practitioner*, **184**, 345. 3 refs.

The author, writing from the Venereal Diseases Clinics of St. Bartholomew's and St. Thomas's Hospitals, London, discusses the part played by homosexuality in the spread of venereal diseases and reviews previous published studies regarding the incidence of homosexuality in clinic populations and of the type of disease from which these patients suffered. He then compares his own experience of this problem in 1954 with that in 1959. In 1954, out of 838 male patients seen at the smaller clinic, ten were homosexual, whereas of 813 patients seen at the same clinic in 1959, forty admitted homosexual contacts, a fourfold increase. Subdivision of the homosexual patients on the basis of individual infections showed that this increased proportion was distributed as follows (the first figure being that for 1954 and the second that for 1959):

- (1) From 0 out of four to eight out of twelve (66.7 per cent.) male patients with early syphilis;
- (2) From five out of 118 (4.3 per cent.) to fifteen out of 136 (11 per cent.) of all males with gonorrhoea;
- (3) From two out of 172 (1.2 per cent.) to eleven out of 241 (4.6 per cent.) of all males with non-gonococcal urethritis;
- (4) From three out of 544 (0.6 per cent.) to six out of 424 (1.4 per cent.) with no detectable venereal disease.

Single men, the majority of whom were in light or sedentary work, predominated among the homosexuals. The figures are analysed statistically.

The evidence supports the general impression that homosexuals are forming an increasing proportion of those attending venereal disease clinics, and that their infections also form a higher proportion of all infections detected. The author points out the need for close questioning regarding sex contacts and the difficulty of diagnosis in men with anal infection. He suggests that public health authorities have a duty to inform the public of the increasing risk of infection arising from homosexuality.

R. S. Morton

Transmission of Venereal Diseases through Homosexual Practices. PRICE, E. R., CLARK, JNR., F. A., HINE, L. W., SHARPE, E. H., and BYRD, J. L. (1961). *Sth. med. J. (Bgham, Ala.)*, **54**, 76. 2 figs, 7 refs.

Medical Problems in V.D. Control. IBARRA, L. M. (1961). *J. Philipp. med. Ass.*, **37**, 20. 8 refs.